REMARKS / ARGUMENTS

In the specification, the first structural formula on page 3, lines 23-30 has been amended to show a nucleoside compound. Support for this amendment is on page 3, lines 20-22, wherein the formulae are referred as "a nucleoside". In the specification, the first paragraph on page 8 has been amended to correct the abbreviations of two compounds and delete the compound which does not appear in the figure described by this paragraph. The titles of Tables 2 and 3 on pages 36 and 37, as well as the referenced within the test to these tables on pages 35 and 37, have been amended to reflect the correct table numbers and to correct typographical errors.

Claims 17-18 and 21-41 are pending in this application. Claims 2-4, 7, 14 and 20 have been canceled without prejudice or disclaimer of any previously claimed subject matter. New claims 21-41 have been added to more clearly define the nucleotide prodrugs which may be used in the invention. Claim 17 has been amended to more clearly define the compounds meant by the term "non nucleoside RT inhibitor". Exemplary "non nucleoside RT inhibitor" compounds are disclosed in the specification on page 6, lines 26-28.

Applicants retain the right to prosecute any unelected or unclaimed subject matter in one or more divisional or continuation applications claiming priority to the above referenced application.

Rejections under 35 U.S.C. §112

The Examiner has rejected claims 2-4, 7, 14, and 17-20 under 35 U.S.C. §112 for failing to comply with the enablement requirement. The Examiner alleges that the specification would not have taught one skilled in the art how to make and use the invention without undue experimentation. Applicants respectfully disagree. The amended claims are limited to methods and pharmaceutical compositions of nucleotide prodrugs of β-L-DDA in combination with selected anti-HIV agents for the treatment of a patient infected with HBV and HIV. The preparation of nucleotide prodrugs of β-L-DDA is disclosed in the specification on pages 18-29. Data on the anti-HBV activity, cytotoxicity and selectivity of an exemplary nucleotide prodrug of β-L-DDA and also the

analogous activity, cytotoxicity and selectivity of compounds which have been used to treat patients is disclosed in the specification in Example 4, on pages 35-36. This Example shows that the nucleotide prodrug of β-L-DDA is significantly more active against HBV than β-L-DDA. Methods for treating a patient infected with HBV by administering an effective amount of a nucleotide prodrugs of β-L-DDA are claimed in the related U.S. Patent No. 6,245,749. Methods for treating a patient infected with HBV by administering a phospholipid prodrug of β-L-DDA 5'-monophosphate are claimed in the related U.S. Patent No. 5,990,093. The declaration of Dr. Jean-Pierre Sommadossi was presented in the prosecution of U.S. Patent No. 5,990,093 and also in the prosecution of U.S. Patent Nos. 6,245,749. Dr. Sommasdossi presents the unexpected finding that the glycosidic bond in β-L-DDA is cleaved in primary hepatocytes which explains the low anti-HBV activity of this nucleoside. Consequently, β-L-DDA does not get significantly phosphorylated to its ddATP form. It was unexpected that β-L-2',3'-ddATP would be a potent inhibitor of woodchuck hepatitis viral DNA polymerase while exhibiting almost no inhibition of human DNA polymerases α, β, and γ (Table 3 on page 37 of the present application). Dr. Sommadossi's declaration presents the finding that the derivative (bis-t-butylSATE) of β-L-2',3'-dideoxyadensosine 5'-monophosphate can elevate the levels of β-L-ddATP in primary hepatocytes in culture to about 250 micromolar (Table 3 of the declaration). Enablement for the effectiveness of nucleotide prodrugs of β-L-DDA against HBV is thus provided.

It was not previously known that one could use nucleotide prodrugs of β-L-DDA in combination with anti-HIV agents to treat a patient infected with HBV and HIV. The administration of such prodrugs in combination with anti-HIV medications for the treatment of patients infected with both HBV and HIV is disclosed in the specification on page 6, lines 18-28. The "second compound" recited in the claims is selected from a list of pharmaceutical agents which are derived from those listed in the specification on page 6, lines 18-28. These compounds are known for their use in the treatment of patients infected with HIV, and are often used in combination with other pharmaceutical agents. The co-administration of the two therapeutic agents in this application is not intended to enhance the effect of either drug. The drug therapeutic indexes for the combinations

described should be determined clinically and are not necessary for enablement of the invention.

The Examiner has noted that "drug-drug interactions are known in the art to have various effects, and when physicians use several drugs in combination, they face the problem of knowing whether a specific combination in a given patient has the potential to result in an interaction" and cites Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 10th Edition, McGraw-Hill Medical Publishing Division, 2001, pages 54-56. The cited passage of this reference also notes that "interactions may be either pharmacokinetic or pharmacodynamic". A pharmacokinetic interaction is the result of a physicochemical interaction between two drugs. β-L-DDA is a nucleoside. The anti-HIV agents proposed for use in the combination therapy disclosed in the specification have been used in combination with other nucleosides. Phosphorylated derivatives of β-L-DDA are not likely to have a physicochemical interaction with other nucleosides or the second compounds recited in the amended claims. A pharmacodynamic interaction can occur in instances wherein the drugs "interact at a common receptor site" or "have additive or inhibitory effects due to action at different sites in an organ." The drugs used in the present application are targeted at two different viruses, HIV and HBV. Thus, the interaction at a common receptor site is not relevant. Furthermore, since these are not intended for the purpose of modulating a human physiological process, such an interaction at different sites in an organ is not relevant. In general, this reference has no relevance for the present application. This reference is relevant when the same physiological processes are being affected by the drugs, but not when the drugs are co-administered to treat different viruses.

Examination of the amended claims and consideration of the arguments presented is respectfully requested.

The Commissioner is authorized to charge any fees not provided herewith, or credit any overpayment associated with this filing to Deposit Account 11-0980.

Respectfully submitted,

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July 27, 2006
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CERTIFICATE OF MAILING

I hereby certify that this Amendment and Response to Office Action along with any documents referred to as attached therein are being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on July 27, 2006.

Nicole Smythe

Date: **July 27, 2006**

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